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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/553,552	04/20/00	LANGER	R 0492611-0326

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EXAMINER	
NGUYEN, D	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/553,552	LANGER ET AL.	
	Examiner	Art Unit	
	Dave Nguyen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election without traverse of species of ortho-ester, species of N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide in the response filed July 19, 2001 has been acknowledged.

With regard to the species restriction of claim 45, applicant's comments are found persuasive and thus, the species restriction of claim 45 has been withdrawn by the examiner.

The prior art of record does not teach or suggest the elected species of N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide. However, the prior art of record has been searched and is found to read on the species of ortho-ester, and compounds embraced by the genus but which specific compounds as taught in the prior art under 35 USC 102(e) do not find a written support from the as-filed specification at the time the invention was made.

Claims 1-45, to which the following grounds of rejection are applicable, are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-45 readable on genera of: 1/ a genus of compounds having one or more hydrolyzable functional moieties, wherein the compound must exhibit the endosomolytic activity in response to a change in pH, 2/ a subgenus of 1/ wherein the compounds further have the ability to mask or encapsulate a lytic agent including a solution of ethanol when not present in an endosome, 3/ a subgenus of 1/ wherein the compounds further have one or more ionizable functional moieties, and wherein the hydrolyzable functional moieties and the ionizable functional moieties function as a whole to lyse the endosome; 4/ a genus of packaging agents that must exhibit the biological activity of complexing directly or indirectly with the compounds of 1/ and of packaging and delivering a desire molecule to the cytoplasm of a cell, and 5/ a genus of non-immunogenic artificial virus less than 150 nm in size that must exhibit the ability to infect and replicating in a cell, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the as-filed specification only provides sufficient written description of monomers having one or more hydrolyzable functional moieties or one or more ionizable moieties so as to exhibit a hydrophobic/hydrophilic transition in response to a change in pH and protonation activity, respectively (page 7 bridging page 8, for example), the as-filed specification does not provide sufficient written description of a representative number of species of polymeric nanoparticles having specific formula or structure so as to exhibit an endosomolytic activity. The as-filed specification only provides sufficient description of an endosomolytic lysing polymer composed of a poly(ortho-esters), wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH. A description of other monomers having hydrolyzable moiety of hydrazone or cis-actonyl is not the same as a disclosure of specific formula or structure of polymeric structure that must exhibit the property of being able to complex with a substance to be delivered into a cell, to transfect a cell through the endosome at a size of less than 150 nm, and to exhibit an endosomolytic activity subsequently thereby releasing the substance into the cytoplasm in an intact form and sufficient amount of the substance for any beneficial utility. Furthermore and with respect to the subgenus of 2/, the as-filed specification contemplates on the basis of its written description that the polymeric nanoparticles can be linked structurally to an endosomolytic functional moiety other than those known in the prior art so that the moiety is only active (released, contacted, and disrupting the lipid bilayers of the endosome) when the polymeric nanoparticles undergo a hydrophobic/hydrophilic transition in response to a change in pH, however, the as-filed specification does not provide any substantial and specific description of the formula or structure representing the subgenus of 2/ and/or a representative number of endosomolytic functional moieties other than those known in the prior art and excluded by the as-filed specification, *e.g.,* chloroquine, fusogenic peptides, inactivated adenoviruses and polyethyleneimine (page 7, second paragraph)

With respect to the subgenus of 3/ which is embraced by the genus of 1/, the specification also does not provide sufficient written description of specific structure(s) and formula of polymeric nanoparticles

comprising monomers having one or more hydrolyzable functional moieties which exhibit a hydrophobic/hydrophilic transition in response to a change in pH, and one or more ionizable functional moieties, which moieties must function to increase the hydrophilicity of the polymeric nanoparticle by protonation in the endosome to the extent that the moieties exhibit an endosomolytic activity (page 9 of the specification).

With respect to claims readable on a genus of packaging agents that must exhibit the biological activity of complexing directly or indirectly with the compounds of 1/ and of packaging and delivering a desire molecule to the cytoplasm of a target cell, the as-filed specification only provides sufficient description of packaging agents composed of cationic polymers either copolymerized with the polymeric nanoparticle of 1/ or forming a mixture with the polymeric nanoparticle of 1/.

With respect to the genus of artificial virus that is non-immunogenic, the as-filed specification does not provide any substantial and specific description of the formula or structure representing the subgenus of non-immunogenic artificial viruses that function as a virus *per se* and yet being non-immunogenic (page 7, second paragraph).

In view of the reasons set forth in the preceding paragraphs, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays (page 11 of the specification) and/or any other unspecified structure containing unspecified compounds and/or packaging agents that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to component(s) with no chemical structure described for the genera of 1/ and/or 2/ and/or 3/ and/or 4/ and/or 5/ because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other

material(s) of compounds other than those known in the prior art, as admitted by the as-filed specification (claim 45) having the biological functions as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of material(s) having hydrolyzable functional moieties, masking and/or encapsulating activities, ionizing elements, and/or packaging agents that must possess the biological properties (importing a desire molecule through the endosome to the cytoplasm of a target cell as a result of endosomolysis) as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of material(s) other than , as contemplated and asserted by the as-filed specification to the extent that those polymeric nanoparticles once formed would exhibit the contemplated biological functions (importing and endosomolytic activities), and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

1) An endosomolytic lysing polymer composed of a poly(ortho-esters) having one or more tertiary amine group, wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH;
2) The polymer of 2/ further comprises a cationic polymer;
3) A cell delivery composition comprising the polymer of 1/ and a compound to be delivered to a cell;
4) A method of employing the lysing polymer of 1/ to lyse an endosome; and
5) A method of delivery a compound to a cell comprising administering the composition of 3/ to a cell.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all structure other than those as indicated in the enabling embodiments, and any other embodiments in the context of artificial virus as claimed in claim 36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of compounds and/or packaging agents and/or artificial viruses), particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended, *e.g.* functions as a delivery vector to deliver any compound to the cell cytoplasm intact through an endosome of cell targeted for delivery.

To the extent that the claims encompass embodiments that meet the written description from the as-filed specification, the specification coupled with the state of the art of record only provides sufficient guidance and/or factual evidence to enable claims readable on an endosomolytic lysing polymer composed of a poly(ortho-esters) having one or more tertiary amine group, wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH.

The as-filed specification contemplates that as long as polymeric nanoparticles comprises a hydrolyzable functional moiety, *e.g.,* ortho-ester, hydrazones and cis-actonyls, and/or an ionizable moiety, *e.g.,* N-methacryloyl-L-histidine, the nanoparticles would exhibit the ability to lyse and/or encapsulate and/or mask any endosomolytic agent (ethanol) so as to lyse an endosome in response to a change in pH thereby releasing a desire compound into the cytoplasm of a cell. The as-filed specification further contemplates that any polymeric nanoparticle can be even used to mask and/or encapsulate volatile organic solvent such as ethanol together with a compound including nucleic acid or RNA to delivered to a cell so that ethanol is released only in an endosome of the cell thereby releasing the compound into the cytoplasm in an intact form so as to perform its biological activity. However, no description of formula or structure of those encapsulating polymers or sufficient guidance as to those encapsulating polymers having an intact core of ethanol is provided by the as-filed specification. While the as-filed specification also provides guidance for the making of one exemplified polymeric nanoparticle, *e.g.,* nanoparticles composed of N-[2-methyl-1,3-O-ethoxyethylidine-propanediol]methacrylamide (protected by an orthoester) that is further used to contain DNA molecules. However, no factual evidence is provided to indicate a successful delivery of the DNA molecules into the cytoplasm of a cell through its endosome in intact forms.

The state of the prior art with respect to the art of employing polymeric compounds other than those disclosed in claim 45 (which compounds are also excluded by the as-filed specification) an a cell delivery/endosomolytic vector remains unpredictable at the time the invention was made. While the making of monomers comprising functional hydrolyzable moieties and/or ionizable moieties is conventional in the prior art of record, the issue is whether or not a skilled artisan would have required an undue

experimentation to identify and/or make the claimed polymeric nanoparticles that exhibit the ability to import a compound into an endosome and subsequently lyse the endosome thereby releasing the compound into the cytoplasm in an intact form. The state of the prior art exemplified by Hope *et al.* (Molecular Membrane Biology, 15, 1-14, 1998) indicates (page 11, column 1):

"Unfortunately, the role of endosome maturation and fusion with lysosomes in the transfection process is unclear. Some reports demonstrate that lysosomotropic agents such as ammonium chloride, chloroquine and monesin inhibit transfection (Gao and Huang 1995), whereas others show that gene transfer (Zabner *et al.* 1995) and oligonucleotide delivery (Zelphati and Szoka Jr. 1997) are either enhanced or their presence [presence of lysosomotropic agents) makes no difference. Consequently, the importance of intracellular processing in the release mechanisms remains to be determined".

More specifically as to even the preferred embodiment of the claimed invention wherein a polymer composed poly(ortho esters) comprising any hydrolyzable functional moiety for use as an delivery and endosomolytic vector, Heller *et al.* (J. of Controlled Release, 13, pp. 295-302, 1990) indicates (page 297, column 2):

"In initial studies [3] using a crosslinked poly (ortho ester) system we found that its acid sensitivity was not adequate, but we also found that increasing the polymer hydrophilicity or decreasing crosslink density did increase acid-sensitivity. Unfortunately, this increase was not sufficient to make this system a useful candidate. However, the acid sensitivity of poly(ortho esters) could be significantly increased by the incorporation of tertiary amine groups into the polymer structure".

Thus, Applicant's contemplation that any polymer compound having any hydrolyzable functional moiety and/or ionizable moiety would import any compound to DNA molecules to an intracellular endosome *in vitro* and/or *in vivo* and subsequently lyse the endosome in response to a change in pH thereby releasing the compound into the cytoplasm in an intact form is supported by neither the state of the art of record or the basis of applicant's disclosure. In fact, even with the established studies on the use of cationic polymers including lipid polymer/DNA complexes to protect, condense, import DNA into an intracellular endosome and mediate DNA escape from the endosome, Pouton CS: Biological Barriers to

gene Transfer. In advanced gene Delivery: From concepts to Pharmaceutical Products, Rollan A, Harwood Press, 1998, pages 65-102, provides factual evidence on page 87 bridging page 88 indicating while polycationic lipid polymers have been used to condense, protect and mediate DNA molecule's transport into an endosome, the polymer was not able to uncouple the DNA in the cytoplasm after endosomolysis, that no gene expression was observed due to the inability of the polymer to uncouple the DNA in the cytoplasm and nucleus, and that control of uncoupling of DNA and condensing agent is a critical process in gene delivery. Pouton CS further indicates on page 88 that "the condensing agent must form a strong enough complex to protect DNA during transport, but must be able to dissociate at the appropriate time, or in the appropriate environment".

In addition, Pouton further indicates on page 88 that understanding and developments of non-viral vectors that can immitate the ability of viruses to exhibit both the ability to mediate endosomal escape and successfully express a gene in the cytoplasm/nucleus remains to be established, and that "cytoplasmic transport is a limitation in non-viral gene delivery but these issues have not been resolved adequately as yet". Furthermore, even two years after the effective filing date of the claimed invention, Hwang *et al.* (Current Opinion in Molecular Therapeutics, 3, 2, pp. 183-191, 2001) teaches:

"A conclusion that can be drawn from polymer-DNA condensation studies is that the size, morphology and charge of the polyplexes [polymer/DNA complexes] generally do no predict the *in vitro* or *in vivo* transfection efficiencies" (page 184, column 1, last paragraph); and

"Thus, the ability to bind and condense DNA into compact structures appears to be a necessary but not sufficient condition to provide efficient gene delivery. Issues such as polymer solubilities, pKA values of the polymer charged groups and DNA binding constants of the polymers must also influence delivery efficiencies. Thus, further work on more detailed physicochemical characterizations are merited (page 184, column 1, last paragraph).

Thus, the as-filed specification does not provide sufficient guidance and/or evidence showing as to how nanoparticle/compound or nanoparticle/DNA complexes that must be of appropriate size to fit inside an endosome (150 nm or less) will be able to lyse the endosome at appropriate time and subsequently

uncouple the compound or DNA in uncondensed and intact form for their biological activity, let alone the problem of *in vivo* transient gene expression by using non-viral vectors, as indicated by the art of record, that does not result into any beneficial effect of the DNA in any of the well-known or disclosed therapeutic utilities as contemplated by the as-filed specification.

To the extent that claims 21 and 42 are readable on a method of nucleic acid therapy comprising the step of administering to any target cell *in vivo* with any of the disclosed pharmaceutical polynucleotide sequence, particularly in light of the specification, the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The application and claims contemplate that any nucleic acid therapy method wherein the claimed endosomolytic composition is employed would generate a pharmaceutical effect in any animal that is in need of the nucleic acid therapy. However, it is not apparent how one skilled in the art employs any of the disclosed endosomolytic compositions in any gene therapy method so as to generate a therapeutically relevant effect. The application does not provide sufficient guidance and/or factual evidence for one skilled in the art to employ any and/or all claimed dendrimer/DNA complexes as nucleic acid therapeutic agent, without undue experimentation. Major considerations for any nucleic acid therapy protocol involve issues that include:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA complexes to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

4/ The fraction of vector taken up by the target cell population, the trafficking of the nucleic acid within cellular organelles, the rate of degradation of the nucleic acid, the level of mRNA produced, the

stability of the nucleic acid product, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced; and

4/ What amount is considered to be therapeutically effective for a nucleic acid therapy method.

In addition, all of these issues differ dramatically based on the specific carrier used, the nucleic acid being used and the disease being treated.

Apart from the problems associated with the ability to import, package, transfect, and lyse an endosome by endosomolytic vectors other than those being enabled (poly ortho-esters having tertiary amine groups) so as to release a sufficient amount of therapeutic DNA inside the cytoplasm of a target cell as indicated in the preceding paragraphs, More specifically as to the lack of reasonable predictability of nucleic acid therapy by using non-viral vectors, Anderson, Nature, Vol. 392, pp. 25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). In addition, Verma *et al.,* Nature Vol. 389, pp. 239-242, 1997, states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, column 1), and that one major obstacle to success has been the ability to deliver genes efficiently by non-viral vectors and obtain sustained expression (page 239, column 3).

Given that *in vivo* nucleic acid therapy wherein any carrier including poly ortho-esters is employed to correct a disease or a medical condition in any and/or all mammals remains unpredictable at the tine the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any or all of the polynucleotide sequences cited in the claims, one skilled in the art would have to engage in a

large quantity of experimentation in order to practice the claimed invention on the basis of applicant's disclosure.

At best, the as-filed specification and the state of the prior art of record only provides a reasonable enablement for claims directed to

An endosomolytic lysing polymer composed of a poly(ortho-esters) having one or more tertiary amine group, wherein said polymer is capable of effecting the lysis of an endosome in response to a change in pH;

The polymer of 2/ further comprises a cationic polymer;

A cell delivery composition comprising the polymer of 1/ and a compound to be delivered to a cell;

A method of employing the lysing polymer of 1/ to lyse an endosome; and

A method of delivery a compound to a cell comprising administering the composition of 3/ to a cell, particularly in view of the disclosure of the as-filed specification and the disclosures of the state of the art of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 is indefinite because it is not apparent as to what is exactly in the method steps or as to how the method steps are positively linked to the introduction of a therapeutic agent as recited in the preamble of the claims, particularly since the method steps do not even recite the step or material(s) having to do with the introduction of a "therapeutic agent". Does applicant intend to employ a nucleic acid as the therapeutic agent or something else? Clarification is requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15, 17-20, 22, 23, 26, 27 and 29-35 are rejected under 35 USC 102(b) as being anticipated by Heller *et al.* (J. Controlled Release, Vol. 13, pp. 295-302, 1990).

Heller *et al.* teach a bioerodible linear polymeric vector comprising a pH-sensitive poly(ortho esters) that has been modified to incorporate tertiary amine groups and insulin, wherein the vector exhibits the insulin releasing activity in response to a decrease in pH at about 5 and 5.5.

Absent evidence to the contrary, the linear vector of Heller *et al.* exhibits any and/or all of the functional activities as recited in the claims.

Claims 17-18 and 26-28 are rejected under 35 USC 103 as being unpatentable over Heller *et al.* taken with Applicant's admission over the prior art of record on page 8 of the specification.

To the extent that Heller *et al.* does not teach poly-orthoester comprising the tertiary amine groups composed of N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide, it would have been obvious to one of ordinary skill in the art as a matter of design choice to have employed poly-orthoesters comprising N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide as a delivery device to deliver insulin because the monomer N-[2-methyl-1,3-O-ethoxyethylidineproanediol]methacrylamide, as evidenced by the as-filed specification, is available in the prior art, and because Heller *et al.* teach that any poly-orthoesters comprising tertiary amine groups would release insulin in response to a change in pH.

Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

To the extent that the claims embrace specifically named compounds that do not find sufficient description on the basis of applicant's disclosure at the time the invention was made, which compounds were disclosed in a US issued patent constituted as prior art under 35 USC 102(e), the following ground of rejection under 35 USC 102(e) is applicable.

Claims 1-12, 15-27, 29-35, and 39-45 are rejected under 35 USC 102(e) as being anticipated by, or in the alternative, under 35 USC 103, as being unpatentable over Bischoff *et al.* (US 6,218,370).

Bischoff *et al.* teach a compound of formula as disclosed on lines 40-50 of column 3 as a packaging and/or endosomolytic vector that is capable of delivering targeting ligands and/or substances including nucleic acids into the cytoplasm of a target cell, *e.g.,* also see column 4, third paragraph for conjugation to targeting ligands, column 5, lines 30-36 as to the teachings of incorporation of polyamine head or functionality in the compound so as to exhibit an endosomolytic activity, column 8, last paragraph as to the teaching of size of less than 100 nm. Column 23 provides working examples showing factual evidence demonstrating successful gene expression by using the compounds.

Absent evidence to the contrary, the delivery method of Bischoff *et al.* anticipates, or the alternative, render the claimed invention *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER